US-PAT-NO: 6093530

DOCUMENT-IDENTIFIER: US 6093530 A

TITLE: Non-calcific biomaterial by glutaraldehyde followed by oxidative
fixation

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The present invention relates to a method of preparing biomaterial for
prosthetic use that has excellent mechanical properties and high calcification
resistance. The method includes the processing of tissues with glutaraldehyde,
by standard methods, to fix the tissue. The method then calls for oxidizing
the tissue using photosensitive dyes or other means. The resulting tissue has
the favorable mechanical properties associated with glutaraldehyde fixation and
the resistance to calcification associated with oxidative fixation.

6. The process of claim 1 wherein the fixation process comprises exposing the
biomaterial to glutaraldehyde in phosphate buffered saline solution for about
12 to 36 hours at a temperature from about 1.degree. to 10.degree. C.,
followed by exposing the biomaterial to glutaraldehyde in phosphate buffered
saline solution for about 12 to 36 hours at a temperature from about 15.degree.
to 30.degree. C., followed by exposing the biomaterial to glutaraldehyde in
phosphate buffered saline solution for about 12 to 36 hours at a temperature
from about 30.degree. to 44.degree. C., and the photooxidation process
comprises exposing the biomaterial to a solution comprising dissolved oxygen
and one or more of a compound selected from methylene blue,

methylene green,
rose bengal, riboflavin, proflavin, fluorescein, rosin, and pyridoxal-5-phosphate, and then exposing the tissue in the solution to light in
quantities sufficient to cause crosslinking of the tissue.

US-PAT-NO: 5746775

DOCUMENT-IDENTIFIER: US 5746775 A

TITLE: Method of making calcification-resistant bioprosthetic tissue

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The overall protein composition and valvular morphology of porcine aortic
valves are unaffected by alcoholic treatment as demonstrated by complete amino
acid analysis and electron spectroscopy for chemical analyses (ESCA). In fact,
alcohol treatment enhances surface smoothing and anisotrophy of porcine aortic
valve leaflets resulting in a surface chemistry which is comparable to fresh
leaflets. In contrast, glutaraldehyde-pretreated (control) or detergent (SDS)
treated tissue show significant differences. Table 5 hereinbelow presents ESCA
data of the surface carbon (C1s), nitrogen (N1s), and oxygen (O1s)
concentrations (%) in porcine aortic valve specimens immersed for 24 hours in
the indicated solution.

US-PAT-NO: 5934283

DOCUMENT-IDENTIFIER: US 5934283 A

TITLE: Pubovaginal sling device

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The cross-linking of the tissues used in the present invention is preferably
accomplished using one or more of the following treatment agents:
glutaraldehyde, dialdehyde, glutaraldehyde starch, dialdehyde starch, an epoxy
compound or ionizing radiation. Certain processes (such as heat, radiation or
pH change) or agents such as halogens, enzymes, organic solvents, detergents,
sodium hydroxide, hydrochloric acid, sodium hypochlorite or hydrogen peroxide)
may be used to inactivate viruses with and without protein coats or to destroy
BSE agent infectivity during the manufacturing process. The tissue may also be
treated with a highly volatile chemical such as for example propylene oxide, to
assist with the sterilization of the tissue. Sterilization may be accomplished
using one or more of the following treatments: glutaraldehyde, alcohol,
propylene oxide or irradiation sterilization. The treatment of the tissue,
with a combination of these materials and processes, can both cross-link the
tissue and render the tissue sterile for implantation.

US-PAT-NO: 5819748

DOCUMENT-IDENTIFIER: US 5819748 A

TITLE: Implant for use in bone surgery

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There are significant differences between collagen fibres at different conditions of maturity. Where the connective tissue is in an active phase of fibrillogenesis, for example during growth or wound healing, collagen fractions can be isolated with different properties. The first fraction is extractable by neutral solutions (neutral-soluble collagen); this consists of recently synthesised tropocollagen molecules which are not aggregated or are only beginning to aggregate. The second fraction is extractable by a sodium citrate solution at pH 3.0, and is thus termed the acid-soluble collagen fraction. The third fraction found in older tissues is the insoluble fraction and can only be extracted by very vigorous methods. One basis for the difference between these fractions lies in the degree of cross-linking by oxidation to produce peroxide bridges. Collagen can also be cross-linked chemically via free amino groups, using aldehydes such as formaldehyde or glutaraldehyde or isocyanates such as hexamethylene diisocyanate. By such cross-linking, animal collagen fractions lose their antigenicity almost completely. Cross-linking of collagen fibrils in this way is for example, made use of in heart replacement surgery, where animal, e.g. porcine, valves are conditioned with glutaraldehyde for use as human pulmonary or mitral valve replacements.

US-PAT-NO: 5697972

DOCUMENT-IDENTIFIER: US 5697972 A

TITLE: Bioprosthetic heart valves having high calcification resistance

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Carpentier teaches that inflammatory reactions including immune reactions and
the degeneration of collagen and elastin are the major factors of malfunction
in bioprosthetic heart valves after transplantation, and suggests a new method
to eliminate these factors for clinical use [A. Carpentier, Biological Tissue
in Heart Valve Replacement, M. I. Ionescu et al. (Eds). Butterworth, London,
1972]. He developed a method for treating the bioprosthetic heart valve to
inhibit any inflammatory reactions by host cells, to maintain or enhance its
strength and flexibility under sterilized conditions, to prevent a degeneration
of collagen and elastin, and to prevent the intrusion of host cells in the
transplanted valve. This method comprises taking a porcine valve aseptically,
washing it with Hanks solution to remove soluble antigenic material, and then
oxidizing mucopolysaccharide and glycoprotein with sodium metaperiodate to form
an aldehyde group on the side chains thereof. The aldehyde group thus formed
may be bound with the adjacent amine group to form an intermolecular
cross-linkage. The remaining sodium metaperiodate is neutralized with ethylene
glycol and then residual amine groups of the glycoprotein molecule are
cross-linked with glutaraldehyde buffer solution. Finally, these
cross-linkages are stabilized by a reduction with sodium

borohydride. However,
this method has disadvantages that the durability of the transplanted valve is
decreased by calcification during the long-term use.

A bioprosthetic tissue of a bovine pericardium was immersed in 200 ml of Hanks
solution (10%) containing H.sub.2 N--PEO400--SO.sub.3 at 4.degree. C. for 2
hours, and reacted with EDC without washing. Then, the tissue in 200 ml of a
1% H.sub.2 N--PEO400--SO.sub.3 NaIO.sub.4 solution was oxidized at 4.degree.
C. for 24 hours, and neutralized at 4.degree. C. for 1 hour in 200 ml of a 10%
H.sub.2 N--PEO400--SO.sub.3 /ethylene glycol solution. The tissue thus treated
was fixed with a glutaraldehyde solution at 4.degree. C. for a week and
reduced with NaBH.sub.4 to prepare BT--PEO400--SO.sub.3.

A bioprosthetic tissue of a bovine pericardium was immersed in Hanks solution
for 2 hours, and then in 50 ml of 2% glutaraldehyde at 4.degree. C. for 24
hours, and washed with a PBS solution. The tissue was added to 50 ml of a 5%
H.sub.2 N--PEO2000--SO.sub.3 solution having pH 11, and the mixture allowed to
react at room temperature for 24 hours. The tissue was washed with a PBS
solution, and added to 200 ml of a 1% sodium metaperiodate (NaIO.sub.4)
solution containing a 1:2 mixture of a 3% NaIO.sub.4 solution and Hanks
solution. The tissue was added to 200 ml of a 1% NaIO.sub.4 solution, and
oxidized at 4.degree. C. for 24 hours in the dark. The tissue was then washed
with a PBS solution, and added to 200 ml of a 1% ethylene glycol solution to
neutralize at 4.degree. C. for 1 hour. The tissue was washed with a PBS
solution, and treated with an acetic anhydride solution to block the unreacted
amine group. The tissue was further reacted with H.sub.2 N--PEO2000--SO.sub.3
using EDC. The tissue thus treated was fixed with a

glutaraldehyde solution
for a week, and reduced with NaBH.sub.4 to prepare
BT--PEO2000--SO.sub.3.

A bioprosthetic tissue of a porcine aortic valve was immersed in Hanks solution
for 2 hours, and then in 50 ml of 2% glutaraldehyde at 4.degree. C. for 24
hours, and washed with a PBS solution. The tissue was added to 50 ml of a 5%
H.sub.2 N--PEO1000--SO.sub.3 solution having pH 11, and allowed to react at
room temperature for 24 hours. The tissue was washed with a PBS solution, and
treated with an acetic anhydride solution to block the unreacted amine group.
Then, the tissue was further reacted with H.sub.2 N--PEO1000--SO.sub.3 using
EDC. The tissue was washed with a PBS solution, added to 200 ml of a 1%
NaIO.sub.4 solution containing a 1:2 mixture of a 3% NaIO.sub.4 solution and
Hanks solution. The tissue was oxidized at 4.degree. C. for 24 hours in the
dark. The tissue thus treated was washed with a PBS solution, and added to 200
ml of a 1% ethylene glycol solution to neutralize at 4.degree. C. for 1 hours.
Then, the tissue was fixed with glutaraldehyde solution for a week, and reduced
with NaBH.sub.4 to prepare BT--PEO1000--SO.sub.3.